Attorney Docket No. 11013.0012-00000

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	)	
	)	
Jay D. KRANZLER et al.	)	Group Art Unit: 1614
	)	
Application No.: 10/623,431	)	Examiner: Alicia R. HUGHES
	)	
Filed: July 18, 2003	)	Confirmation No.: 4067
	)	
For: METHODS OF TREATING FIBROMYALGIA SYNDROME, CHRONIC FATIGUE SYNDROME AND PAIN	)	

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

DECLARATION UNDER 37 C.F.R. § 1.132

I, Srinivas Rao, do hereby make the following declaration:

1. I currently hold the position of Chief Scientific Officer at Cypress Biosciences. I have held this position since July of 2001. My previous position at Cypress Biosciences was Director of Science & Technology, which I held from January 2001 to July 2001. Prior to that, I worked as a consultant for Cypress Biosciences from August 2000 to January 2001. Prior to joining Cypress Biosciences, I practiced medicine as an intern in Internal Medicine at Yale-New Haven Hospital from 1998-1999.

2. I received a Doctor of Philosophy degree in Neurobiology from Yale Graduate School in 2000. I received a Doctor of Medicine degree from Yale School of Medicine in 1998. I also hold a Master of Science degree in Electrical Engineering,

awarded by Yale Graduate School in 1991, and a Bachelor of Science degree in Electrical Engineering, awarded by Yale College in 1990.

3. I have authored or co-authored over half a dozen scientific articles related to the treatment of Fibromyalgia.

4. One of my responsibilities at Cypress Biosciences is the design, execution, and management of preclinical research programs and pre-Phase III clinical programs.

5. I have read and understand the Office Action issued by the United States Patent and Trademark Office on November 27, 2009, in the above referenced application. I have also read and understand United States Patent Number 6,441,038 to Loder ("Loder"), which was cited in the Office Action.

The claimed methods of treatment differ from Loder in several respects

6. Loder discloses methods for treating conditions of fatigue, pain, weakness and mood that are associated with neurological disorders, such as fibromyalgia, chronic fatigue syndrome and stroke. The treatments described by Loder require administering an inhibitor of noradrenaline reuptake together with a neurotransmitter precursor such as phenylalanine or tyrosine. Moreover, Loder specifically focuses on the use of selective inhibitors of noradrenaline, such as lofepramine, desipramine, and reboxetine, in combination with a neurotransmitter precursor. There is no teaching in Loder of treating any condition using only an inhibitor of noradrenaline uptake.

7. Case History #1 describes a woman suffering from chronic fatigue syndrome associated with fibromyalgia and irritable bowel syndrome. See Loder col. 5 lines 40 - 65. "She was given almost all conceivable treatments over the years including

many types of non-steroidal anti-inflammatory drugs, both tricyclic and serotonin reuptake inhibiting and noradrenaline reuptake inhibiting antidepressants, and even steroids." Loder indicates that some of these treatments produced transient effects but they never lasted. The patient was then given combined treatment with the selective noradrenaline reuptake inhibitor lofepramine and the neurotransmitter precursor phenylalanine. Over a period of two to three weeks she experienced a considerable improvement in fatigue, in fibromyalgia and in her irritable bowel. Thus, it is clear that the treatments described by Loder require administering an inhibitor of noradrenaline reuptake together with a neurotransmitter precursor. Furthermore, Loder specifically teaches that monotherapy treatments are ineffective.

Our robust efficacy findings of administration of milnacipran monotherapy in pain are surprising and unexpected.

8. Clinical trials have shown that administration of milnacipran monotherapy to patients substantially decreased chronic pain associated with fibromyalgia. In one recent Phase III clinical study, milnacipran administered at 200 mg/day to patients suffering from fibromyalgia was reported to have led to *significant* improvements over placebo lasting for fifteen weeks. *See* Exhibit A at page 6. In this study, and another Phase III study, 100 and 200 mg/day doses of milnacipran were reported to *rapidly* reduce pain in patients suffering from fibromyalgia, with *significant* effects observed after one week of treatment. *Id.* The results of both of these studies are summarized in Figure 1a and Figure 1b below.

Figure 1a

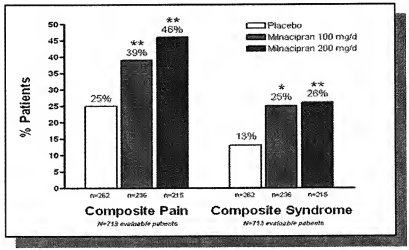
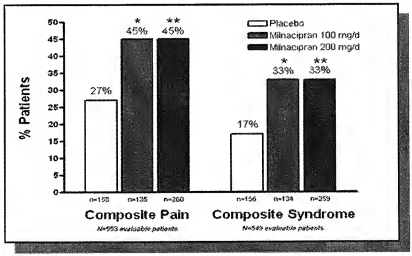


Figure 1b



**P<.05, vs. Placebo; **P<.001, vs. Placebo*

Pain Responder: Pain (≥ 30% VAS improvement in PED 24-hr pain recall) AND global status (PGIC = 1 or 2); Observed Cases (OC)

Syndrome Responder: pain responder criteria PLUS physical function (≥ 6 point improvement in SF-36 PCS); Observed Cases (OC)

9. Also in clinical trials, milnacipran monotherapy treatment of fibromyalgia surprisingly demonstrated a durability of response of up to 1-year. A long-term Phase III clinical trial of milnacipran treatment in fibromyalgia patients showed that patients receiving continuous 12-month treatment with milnacipran at 100 mg/day and 200 mg/day doses experienced 39-46% improvement in 24-hour recall pain scores, and 41-47% improvements in 7-day recall pain scores. *Id.* at pages 6-7. As described in Figure 1a above, patients that received milnacipran for six months reported a decrease in pain. Moreover, as seen in Figure 2a below, where those patients continued to use milnacipran for an additional six months, the decrease in pain was maintained for the entire twelve-month treatment period. Figure 2b shows that patients who were treated with placebo for the first six-months of the study, followed by treatment with milnacipran in the second six-months, reported substantial improvement in pain once the milnacipran treatment was initiated.

Figure 2a

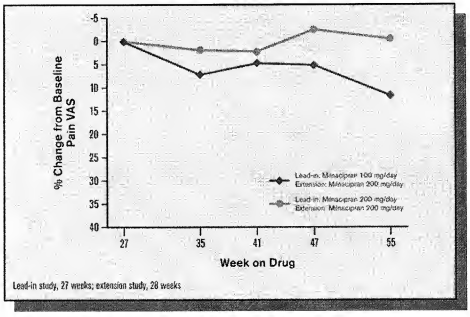
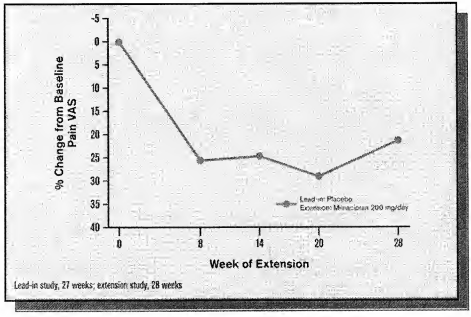


Figure 2b



10. Similarly, a European clinical trial evaluating the efficacy of milnacipran dosage of 200 mg/day in fibromyalgia patients for twelve weeks reported *significant* improvements in both 24-hour recall pain and 7-day recall pain. *Id.* at page 7. These sustained, significant reductions in pain are also surprising.

11. Milnacipran has also been surprisingly shown to be an effective treatment for neuropathic pain, such as diabetic peripheral neuropathic pain (DPNP). Neuropathic pain is pain that is initiated or caused by a primary lesion or dysfunction in the nervous system. Clinical conditions that meet the definition for peripheral neuropathic pain include DPNP, postherpetic neuralgia (PHN), trigeminal neuralgia, and certain subsets of chronic low back pain.

12. Standard animal models for neuropathic pain states include the Chung model (spinal nerve ligation), the Bennet & Xie model (chronic constriction injury), and the Seltzer model (partial sciatic ligation). *See* Exhibit C at page 9.14.1. King *et al.* used a spinal nerve ligation animal model to examine the effectiveness of milnacipran to treat neuropathic pain states, such as DPNP. *See* Exhibit D. King *et al.* showed that administration of milnacipran effectively reversed spinal nerve ligation-induced thermal and tactile hypersensitivity, as well as shift in weight bearing, thus showing milnacipran to be a highly effective treatment for neuropathic pain states, such as DPNP.

13. In particular, spinal injection of milnacipran into rats in which the L5/L6 spinal nerve had been ligated was shown to *reverse* SNL-induced thermal hypersensitivity and SNL-induced tactile hypersensitivity. *Id.* at page 515. Spinal injection also attenuated shift in weight bearing associated with the SNL injury. *Id.* Subcutaneous injection provided an acute *reversal* of SNL-induced thermal

hypersensitivity lasting greater than five hours. *Id.* at pages 515-516. After three days of administration, the reduction in SNL-induced thermal hypersensitivity became chronic, not just acute. *Id.* at page 517. Although subcutaneous injection of milnacipran did not have an acute affect on weight-bearing distribution associated with SNL-injury, it did provide a chronic improvement in equalizing weight-bearing after five days of administration. *Id.* These substantial decreases in neuropathic pain associated with administration of milnacipran are surprising and unexpected.

14. Thus, the data described above establish that milnacipran has been surprisingly and unexpectedly successful at treating various pain states, including neuropathic pain, such as DPNP, and the chronic pain associated with fibromyalgia.

The results of the simultaneous administration of milnacipran and pregabalin in patients with fibromyalgia who had an inadequate response to pregabalin alone are unexpected.

15. Finally, a recent phase III clinical trial showed that treatment with milnacipran in combination with pregabalin can lead to substantial improvement in patients suffering from fibromyalgia. Exhibit B at page 3. The combination resulted in a surprising and unexpected increase of the response rate over pregabalin alone. These results are particularly surprising considering the patient population was, by definition, drug resistant. *Id.* at pages 7-9. Moreover, synergy between drugs of different pharmacological classes has never been demonstrated between any two agents in fibromyalgia.

16. In summary, the data described above establish that milnacipran is surprisingly and unexpectedly effective at treating fibromyalgia and neuropathic pain

states, including diabetic peripheral neuropathic pain (DPNP). In addition, the combination of milnacipran with pregabalin leads to substantial improvement in patients suffering from fibromyalgia. These results are surprising and unexpected and could not have been predicted from the teachings of the prior art.

17. I hereby declare that all statements made herein are of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of this application or any patent issuing thereon.

Dated: April 13, 2010 By: _____
Srinivas Rao, M.D., Ph.D.